

## Remarks

Claim 8 is amended.

Claims 1, 3-6, 8 and 11 are pending.

### 35 USC 112, second paragraph

Applicants have amended to make claim 8 depend from claim 1. Thus this rejection is overcome.  
No new matter is added.

### Rejection

Claims 1-6 and 9-11 are rejected under 35 USC 103(a) as being unpatentable over Struillou, EP 0752465 in view of Hirota, JP2002220380, English Translation provided by the Office.  
Applicants thank the Office for providing a copy of the Machine Translation for JP2002220380.

The Examiner alleges that Struillou discloses a method for controlled release of biologically active hydroxyl group containing substances. Office agrees that Struillou differs from the instant claims as it does not disclose the specific claimed diamine.

Thus Office relies on Hirota. Office alleges that Hirota discloses a method of forming an antibiotic drug by mixing an amino acid (Office believes this meets the limitation of the claimed "biologically active hydroxyl group containing substance") with a carboxylic acid halide compound and then the addition of a tertiary amine such as 1,2-bis(dimethylamino)ethane to form an ester.

The Office's rationale for the combination "It is obvious to replace one component for another equivalent component if it is recognized in the art that two components are equivalent and is not based on the Applicant disclosure". See *In re Ruff*, 256 F.2d 590, 118USPQ 340 (CCPA 1958)". See page 5 of Final Rejection, mailed on May 13, 2010.

Applicants respectfully traverse the above rejection.

Whether a claim is obvious is based on an objective analysis of the scope and content of the prior art, the differences between the prior art and each element of the claimed invention, and the level of skill in the pertinent art. See *Graham v. John Deere Co.*, 383 U.S. 1, 15-17 (1966).

The Office has failed to meet its burden to establish a *prima facie* case of obviousness at least for the following reasons:

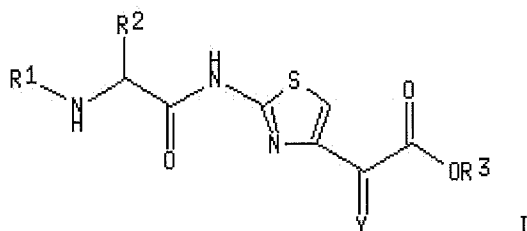
- Office believes that the amino acid taught in Hirota meets the limitations of the claimed "biologically active hydroxyl group containing substance". A hydroxyl group cannot in any sense be considered the same as a carboxylic acid group. Further, the acid functionality of the carboxylic acid group of the amino acid is not reacted with a halogen-substituted aliphatic carboxylic acid halide yielding a halogen-substituted ester as presently claimed. The acid of the amino acid is not reacted to form an ester but instead is reacted to form an amide.
- The Office's rationale that 1,2-bis(dimethylamino)ethane is an equivalent to tertiary amines such as triethylamine or dimethylalkylamine as in Struillou lacks basis in fact. A patent for a combination which only unites old elements with no change in their respective functions would of course be obvious. However, 1,2-bis(dimethylamino)ethane used in Hirota has an entirely different function/purpose from the amines taught in Struillou.
- The references to be combined as proposed by the Office, there must be some showing that there would have been an expectation of success in the combination and that the combination would result in predictable results. No such showing can be provided from the cited references.

Specifically Hirota teaches that amidothiazole esters are prepared by condensation of  $R_1NHCHR_2CO_2H$  with 2-aminothiazole esters using carboxylic acid halides and tertiary amines as condensing agents.

Applicants attach a Chemical Abstract of the Hirota reference which is more easily understood than the machine translation provided by the Office. The abstract clarifies the functions/purposes of the amino acids and the tertiary amines.

L1 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2010 ACS on STN  
AN 2002:591943 HCAPLUS  
DN 137:140517  
TI Preparation of amidothiazole esters as intermediates for cephalosporin antibiotics  
IN Hirota, Yoshihiro; Matsunaga, Tomonori  
PA Tokuyama Corp., Japan  
SO Jpn. Kokai Tokkyo Koho, 12 pp.  
CODEN: JKXXAF  
DT Patent  
LA Japanese  
FAN.CNT 1

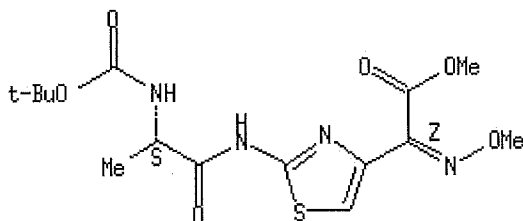
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	<u>JP 2002220380</u>	A	20020809	<u>JP 2001-17849</u>	20010126
PRAI	<u>JP 2001-17849</u>		20010126		
OS	CASREACT <u>137:140517</u> ; MARPAT <u>137:140517</u>				
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AB Amidothiazole esters I [R1 = protective group; R2 = H, C1-6 satd. hydrocarbyl, C2-10 unsatd. hydrocarbyl; R3 = C1-7 alkyl, C7-11 aralkyl; Y = NR4, CHR5, H2; R4 = C1-7 alkyloxy, C7-19 aralkyloxy; R5 = H, C1-7 alkyl(oxy), C7-19 aralkyl(oxy)] are prepd. by condensation of R1NHCHR2CO2H (R1, R2 = same as I) with 2-aminothiazole esters using carboxylic acid halides and tertiary amines as condensing agents. N-tert-butoxycarbonyl-L-alanine was amidated by Et 2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetate in CH2Cl2 in the presence of NEt3 and o-toluoyl chloride at -20° for 2 h to give 84.7% (Z)-I (R1 = CO2Bu-tert, R2 = Me, R3 = Et, Y = NOME).

As can be seen from the abstract, the amino acids (which Office incorrectly believes meets the limitations of the present claims as an hydroxyl group cannot be considered the same as a carboxylic acid group) are not used to form a halogenoacetate ester as presently claimed. The aminoacid (i.e. N-tert-butoxycarbonyl-L-alanine) is **amidated** by the amidothiazole ester. The aminoacid reacts with the amine on the 2-aminothiazole to form an **amide** not an ester.

The intermediates formed resemble the compound below:



As can be seen an amide is formed, not an ester.

The Office then goes on to explain that the tertiary amine in Hirota may easily replace the amines used in Struillou. However, as evident from the abstract above and the machine translation provided by the Office, the amines in Hirota do not form covalent bonds with the amidothiazole esters but

instead function as a condensing agent in combination with the acid chloride. It is clear from the examples of Hirota, ie. paragraph [0079], that the protected amino acid is reacted with an acid chloride in the presence of a tertiary amine in order to form an intermediate anhydride which goes on to **amidate** the 2-(2-aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate. The acid chloride reaction with the tertiary amine serves to eliminate water. The tertiary amine's function is to capture the HCL formed in the reaction of the protected amino acid with acid chloride. **Accordingly the tertiary amine of Hirota does not end up forming a covalently bound water soluble salt but serves to trap HCL.**

Thus it makes no sense to select from Hirota any of the tertiary amines and use in the method of Struillou. The tertiary amines of Hirota are used in the well know capacity as HCL traps. In contrast Struillou teaches formation of covalent bonds with tertiary amines by reaction with a halogen-substituted ester. Accordingly, the Office's rational that this is simply a combination which only unites old elements with no change in their respective functions has no basis in fact.

Respectfully, the Office appears to have selected a secondary reference, believing that the reference teaches steps a) and b) instantly claimed. However, as explained above this is incorrect. There is no reaction of an hydroxyl group with a halogen-substituted aliphatic carboxylic acid halide yielding a halogen-substituted ester. There is no formation of a water-soluble ammonium salt containing ester from the ester from step a) by reaction of the ester from step a) with a diamine. The amines of Hirota and Struillou have very different functions so that substitution of those amines taught in Hirota for the amines taught in Struillou is not simply substitution of one equivalent for another performing the same function.

For the references to be combined as proposed by the Office, there must be some showing that there would have been an expectation of success in the combination and that the combination would result in a predictable results. No such showing has been provided from the cited references.

Applicants respectfully submit all objections and rejections are addressed and are overcome and kindly ask that they be withdrawn and that claims 1, 3-6 and 11 be found allowable. In the event that minor amendments will further prosecution, Applicants request that the examiner contact the undersigned representative.

Respectfully submitted,

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